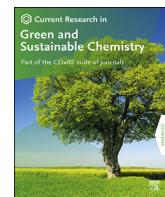




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## Natural products as environmentally safe and green approach to combat Covid-19



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### ABSTRACT

The Covid-19 pandemic is a major catastrophe in recent times that has taken a toll over the global scale in terms of the casualties, economic impact, and human beings' lifestyle. Scientists and researchers worldwide are dedicated to counter this issue using large-scale drug discovery and analysis to explore both the vaccination and the cure for Covid-19. However, almost all of the tested medicinal options cover allopathic medicines. A major issue associated with the above approach is the side effects that present a lacuna in arriving at an agreeable solution. To date, a total of >160,000,000 Covid-19 cases have been reported. However, to date, there is no report available on the scope and application of natural medicines in the treatment of the Covid-19. This review aims to target this area while covering the economic and other impacts of the Covid-19 on human life, the significance of greener solutions in countering drug development, and the possible solutions of the Covid-19 using herbal drug treatment.

### 1. Introduction

The Covid-19 pandemic has considerably affected nations all across the world. Within the span of a year and a half, this issue has drawn the attention of worldwide scientists and researchers to explore and achieve the possible solutions in the course of both prevention as well as a cure [1,2]. Accordingly, the research in this area has been devoted to finding a suitable vaccination and arriving at a cure for this disease. Conventionally for viral infections, chemical medicines have been the most sought-after strategy [3]. However, the usage of the conventional synthetic organic compound-based allopathic medicines for treatment has come under some criticism in the past few years—the primary reason being the numerous side effects of such medicines. To counter the side effects of the allopathic medicines, it is often prescribed by the physician to consume multiple drugs. The overall influence on the human body becomes complex. Another issue is that the prolonged usage of the allopathic medicines renders the human body to develop immunity against these drugs, requiring stronger doses of these medicines that are not considered healthy to the body [4–6].

Over the years, it has been observed that the chemical extracts from natural products or so-called herbal medicines have been found to be effective against a number of diseases. This ranges from antimicrobial,

antifungal, antimalarial, antiviral, anticancer, anti-HIV, etc. [7,8]. A major reason why the chemical medicines have been the most sought after is their quick action against the targeted disease. On the other hand, herbal drugs have been criticized for their comparatively slower action on the human body. However, a significant plus point associated with herbal medicines is their benign nature, which is significantly less likely to affect humans in any negative manner.

In the past few months, several articles have come across the literature describing the possible strategy to counter the Covid-19 pandemic [9–14]. However, all of them describe the treatment of the pandemic or potential vaccine using chemical medicines. To date, there is no research available in the literature on the application of herbal medicines in the treatment or possible vaccines for the Covid-19. The present article summarizes the chemical medicines and vaccines that have been proposed to counter the Covid-19. Some of the economic impacts of the Covid-19 have also been covered, and the overall impact of the Covid-19 on the life of human beings worldwide has been analyzed. Some of the green approaches for drug development have been discussed. A review of literature is presented on the use of herbal medicines that have been used to counter infectious diseases. It is postulated that in addition to the currently being investigated allopathic drugs and vaccines, herbal medicines could also be a possible solution to the pandemic.

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## 2. A brief overview of the Covid-19

### 2.1. An introduction to the coronavirus

Human beings generally face a lot of pathological infections. In this context, the common pathogenic organisms of infectious diseases are primarily viruses [15], the latest being the Covid-19 [1,2]. There are almost 10,000 types of viruses known, although only a few are well recognized. Several commonly occurring viruses cause respiratory infections, including the influenza-related virus, human metapneumovirus, enterovirus, measles virus, herpes simplex virus, coronavirus, adenovirus, cytomegalovirus, etc. [16]. Since the onset of avian influenza, many viral infections have been sprouted in recent years [17]. The coronavirus was not usually widely recognized due to its weak affiliations with human beings. However, after the widespread SARS, the coronavirus received significant recognition. The bats have been reported to be one of the most common hosts of the coronavirus and were also the cause of the SARS and the MERS (Middle East respiratory syndrome) [18,19]. Including the SARS-CoV-2, there are around seven known kinds of the known coronaviruses that are contagious. Human coronavirus 229E, human coronavirus OC43, and human coronavirus NL63 are the commonly occurring coronaviruses that cause the cold to humans, although with considerably greater serious effects compared to the common cold [20]. However, it has now been recognized that the SARS and the Covid-19 have a serious influence on the human society. The WHO named the present virus the SARS-CoV-2, and it has a diameter of around 60 to 140 nm.

### 2.2. Covid-19 infection and the pandemic

The coronavirus disease-2019 (Covid-19) is caused by severe acute respiratory syndrome (SARS)-CoV-2 virus (Fig. 1) [21,22]. It has been reported to have originated from Wuhan city of China, which is the capital of the Hubei province [23]. The SARS-CoV-2 is an enveloped RNA virus. Currently, it has been recognized that the Covid-19 mainly transfers from one patient to another human being [24,25]. There are mainly two modes of transmission that have been identified, (i) respiratory droplet transmission and the (ii) close contact transmission. With a single sneeze of human beings, around 40,000 saliva droplets erupt, and approximately 30,000 droplets come out with the coughing. Each of these saliva droplets contains almost 20,00,000 (20 lakh) of the coronaviruses, which then can float in the air along with the dust particles. This way, the coronavirus becomes airborne and enters the human body through the nose and mouth when the humans intake the virus-containing air or through other body parts depending upon the contact of the body with the surfaces having the adsorbed coronavirus. Therefore, the virus gains entry to the human body and primarily causes

the infection to the lungs. Our lung cells contain the ACE2 Receptors (Fig. 2), and the spikes of coronavirus have a better capacity of binding with these receptors. This process of the entry of the virus inside the lung cells is known as endocytosis. Thereafter the virus becomes uncoated, and its RNA becomes free for replication. The entry of the coronavirus through the ACE2 receptors results in the hijack of the cell function by which it can form numerous new viruses. By replication, transcription, and translation, new viruses assemble and are released by exocytosis. The virus causes damage to the DNA of the host cell and causes the release of toxic molecules (Fig. 3), which affects the immune system. A possible mechanism of virus infection to the brain and the nerve cells is shown in Fig. 4. On the global level, vaccinations have started, and many people have received the vaccines. However, till May 10, 2021, there are a total of >160,000,000 Covid-19 cases reported worldwide. The total number of deaths that have been reported is > 3,300,000, and a total of >140,000,000 people have recovered so far. A large number of cases and casualties were reported last year in Europe and the USA. USA, India, Brazil, France, Turkey, Russia, UK, Italy, Spain, and Germany have shown the highest number of cases. To date, the highest number of cases (>33,000,000) and the highest number of deaths (>599,000) have been reported in the USA. Currently, India is facing the second wave of Covid-19, and nearly 350,000 new cases are being reported daily, whereas close to 4000 deaths are taking place each day.

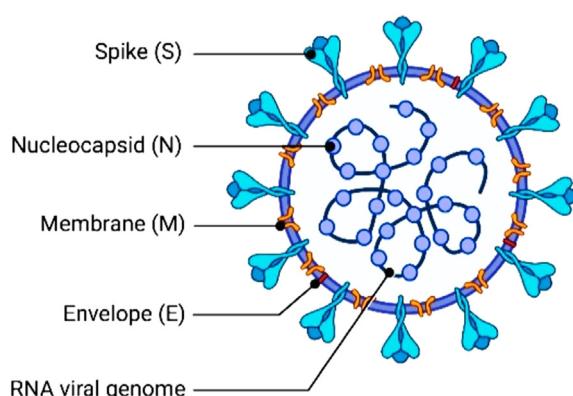
### 2.3. Economic impact of Covid-19

The first and foremost influence of the Covid-19 pandemic worldwide is on the stock markets, especially on Feb 24, 2020. Almost all of the major economies have received a crushing downfall due to the pandemic [26]. In addition, the growth rate of the GDP has suffered considerably [27]. There has been economic, social, and political instability and unrest in these times worldwide. An acute shortage of food worldwide, and a spike in the price of the goods, market disruptions has occurred. The education sector has suffered a great deal due to the outbreak of the Covid-19 pandemic [28]. Another significant influence of the pandemic has been the cancellation/postponement of international gatherings such as global conferences, sporting events, fashion extravaganza, etc. The cinema halls have received closures, and so do the great and big business shopping malls, and the entertainment industry overall has received a setback. There has also been a disruption in the area of agriculture. The timely harvest of crops and the proper distribution of the food to the markets has not been functional on a regular basis due to the government rules on lockdowns and social distancing. The transportation industry related to aviation, cruise liners, train, bus, etc. sectors has also been practically stopped from work. The tourism sector, restaurant sector, gambling, and betting, etc., areas have also received drastic falls. There has been a global surge in unemployment due to the continuous periods of lockdowns. On the international level, there has been the closure of business and the loss of production and distribution.

## 3. Current investigated drugs and vaccines and their activity against the Covid-19

### 3.1. Drugs for the treatment of Covid-19

The coronavirus modifies its strain continuously, and therefore, there are no hundred percent effective drugs and active vaccines known until now. Some antibiotics, antiviral, plasma, and other medical treatments are currently in practice to treat the Covid-19 (Fig. 5). Antibodies function by locking the spike of virus and inhibiting their entry. The convalescent plasma also works in the same way. The drug chloroquine [14,29], hydroxychloroquine [13,30], and Umifenovir [31] inhibit the uncoating of the virus. The drug hydroxychloroquine gained special attention during the pandemic. There was strong scientific evidence supporting the utility of this drug in the control of the Covid-19, while its



**Fig. 1.** Structure of SARS-CoV-2 <https://www.biophysics.org/blog/coronavirus-structure-vaccine-and-therapy-development>.

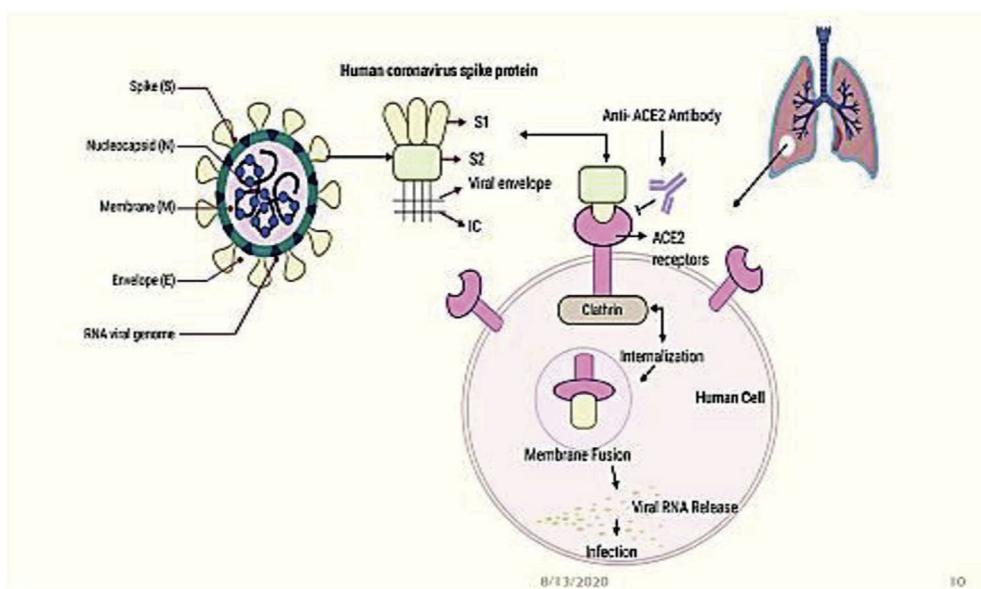


Fig. 2. Entry through ACE2 Receptors in lungs [122].

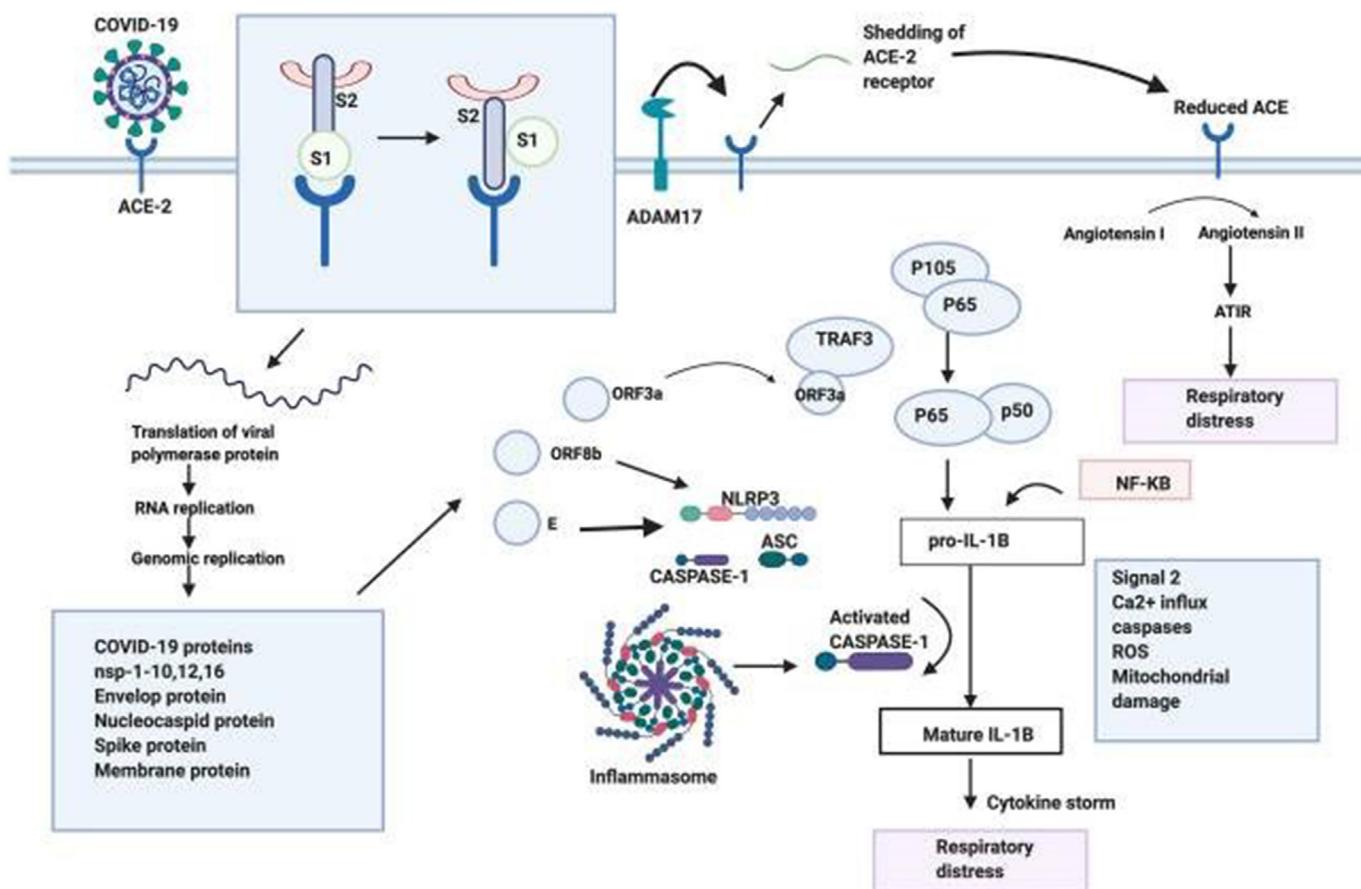


Fig. 3. Replication of virus in cell and toxic molecule release [122].

usage was not approved by the FDA. Although even after a substantial initial promise, the WHO announced the stopping of the drug trials. Lopinavir, Ritonavir [32,33], Remdesivir [34], Darunavir [12], Ribavirin [35], Favipiravir [11], and Glycyrrhizin [9] inhibit virus replication. The

Glycyrrhizin also inhibits toxic molecules. Disulfiram [36] inhibits the release of toxic molecules. Oseltamivir [37] inhibits neuraminidase enzyme, which inhibits exocytosis. A list of some of the drugs that have been evaluated against Covid-19 is shown in Table 1.

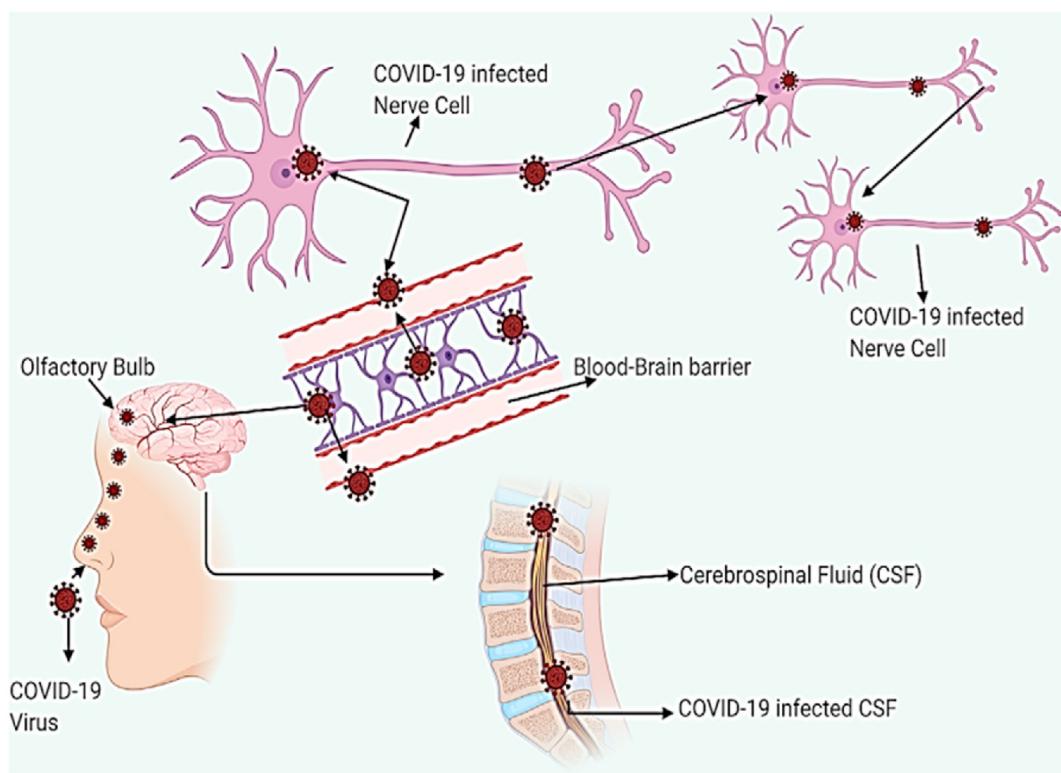


Fig. 4. Viral infection in brain and nerve cells [122].

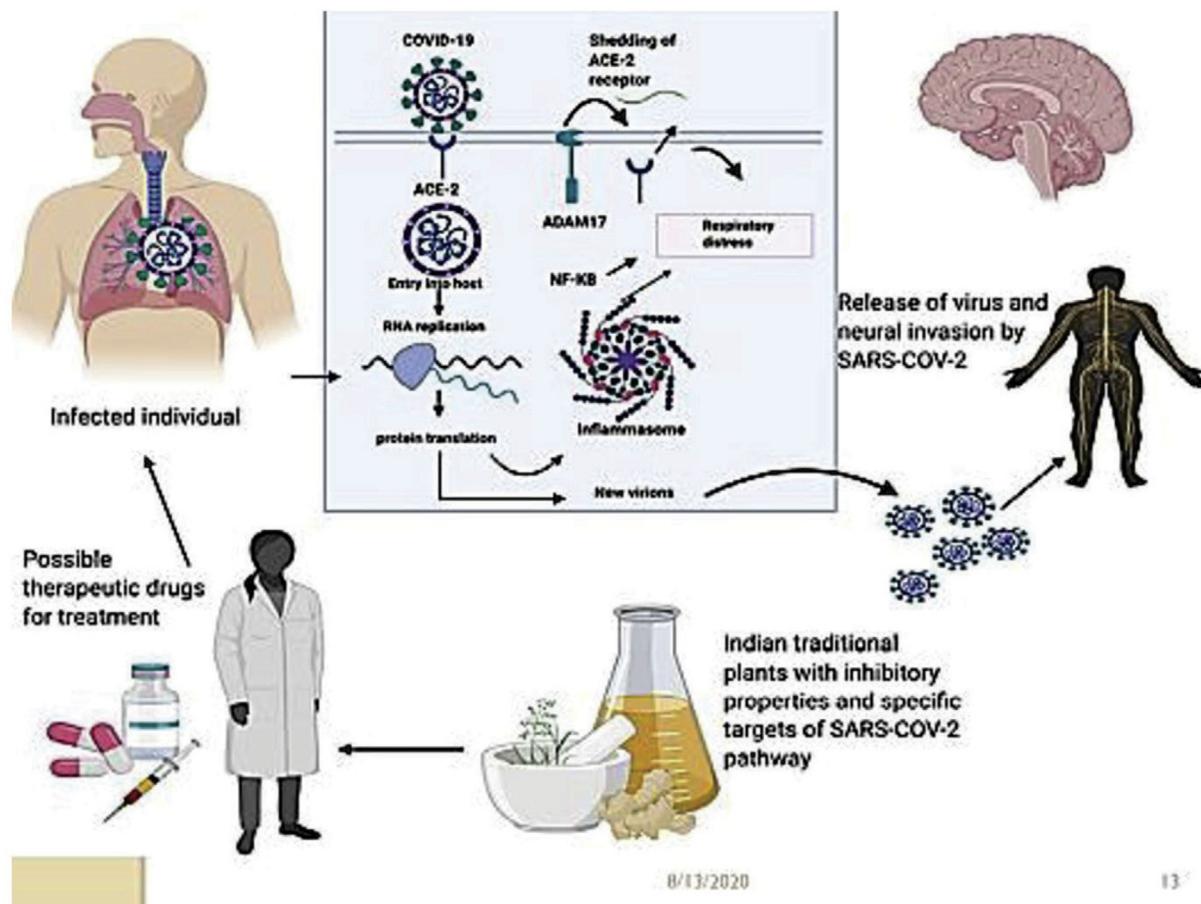
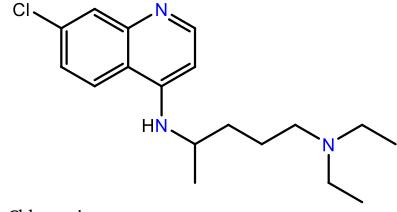
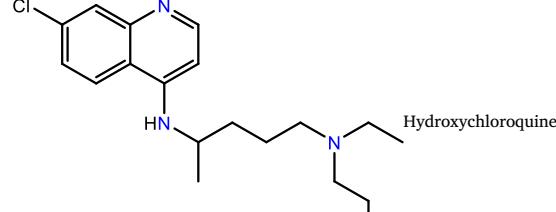
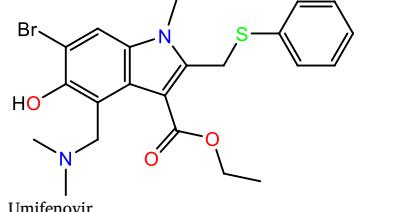
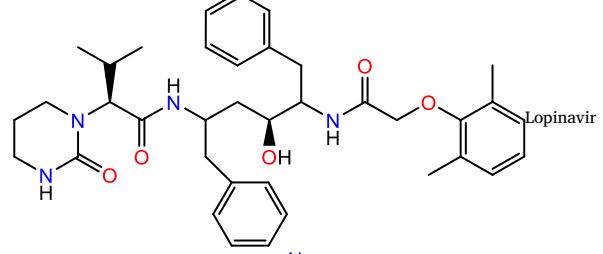
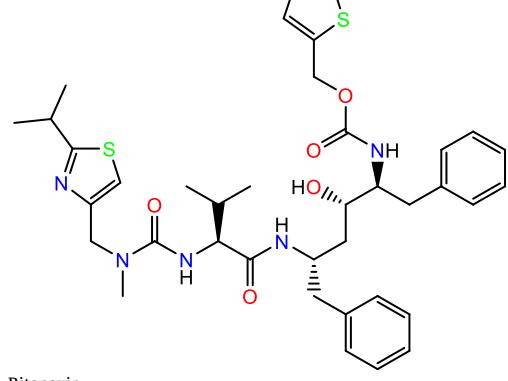


Fig. 5. Possible Treatment of COVID-19 by targeting viral replication stages [122].

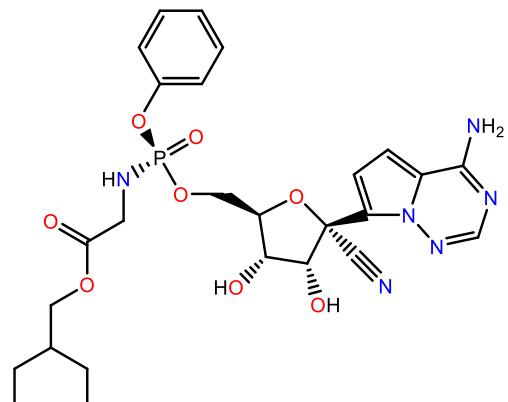
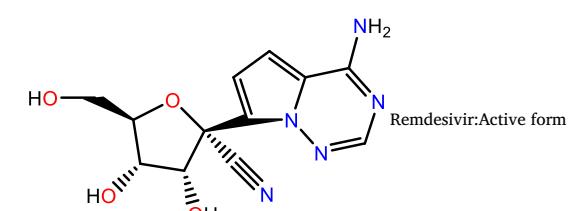
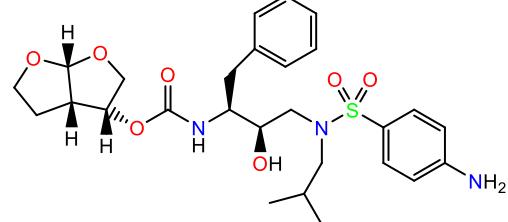
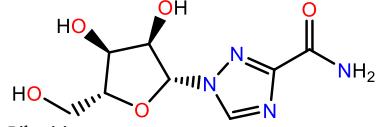
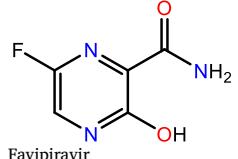
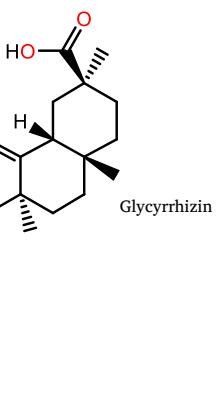
**Table 1**

Some of the drugs that have been tested against Covid-19.

Structure and name of drug	Remarks
	It is old antimalarial drug, recently reported as a potential antiviral drug. It has antiviral action against SARS-CoV-2. Inhibit entry and uncoating of virus. Side effects: blurred vision, nausea, vomiting, diarrhea, headache
	Antimalarial drug has similar antiviral action against SARS-CoV-2. It is less hazardous than chloroquine. It inhibits entry and uncoating of virus.
	It is also known as Arbidol and may have potential to treat COVID-19. Arbidol impedes trimerization of SARS-CoV-2 spike glycoprotein. It inhibits entry and uncoating of virus
	Lopinavir is antiviral; drug Mechanism: acting as viral protease inhibitor, currently used against HIV. It is effective against SARS-CoV-2 when used in combination with ritonavir. It inhibits replication of virus in host cell. Common side effects: diarrhea, headache, vomiting, nausea, etc.
	Similar to lopinavir, ritonavir is also an antiviral currently used against HIV. It has also potential against SARS-CoV-2 when used in combination with lopinavir. It inhibits replication of virus in host cell It has similar side effects as that of lopinavir.
Ritonavir	A nucleoside analog. It was prepared for treatment of Ebola Virus. It inhibits replication of virus in host cell. RDV is prodrug becomes active in side human cell for Covid-19. Side effects: Liver damage, nausea, vomiting RDV's Active metabolite, GS-441525. It inhibits replication of virus in host cell

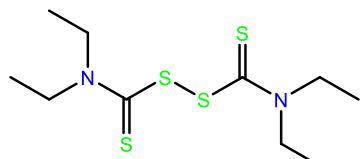
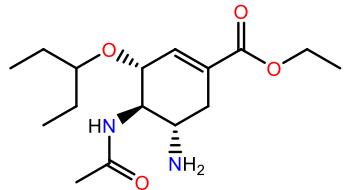
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**Table 1 (continued)**

Structure and name of drug	Remarks
 Remdesivir: Prodrug	
 Remdesivir: Active form	
 Darunavir	Darunavir is being studied as a possible treatment for SARS-CoV-2. It is protease inhibitor. The coronavirus responsible for COVID-19, due to <i>in vitro</i> evidence supporting its ability to combat this infection. Clinical trials are underway and are expected to conclude in August 2020. It inhibits replication of virus in host cell
 Ribavirin	Ribavirin is a nucleoside analog antiviral agent. For treatment of COVID 19 its high concentration is needed than remdesivir. It inhibits replication of virus in host cell The common side effects: nausea, fevers, inflammation, headache etc.
 Favipiravir	Favipiravir is a prodrug antiviral agent. RdRp inhibitor, RNA induced Lethal Mutagenesis. It inhibits replication of virus in host cell Side Effects: During pregnancy may result in harm to the baby.
 Glycyrrhizin	Glycyrrhizic acid is extracted from the root of the licorice plant; <i>Glycyrrhiza glabra</i> . It is a triterpene glycoside with glycyrrhetic acid that possesses a wide range of pharmacological and biological activities. It inhibits replication of virus in host cell and inhibits toxic molecule release
	Disulfiram blocks an enzyme that is involved in metabolizing alcohol intake. In Covid-19, inhibits toxic molecule release. Disulfiram produces very unpleasant side effects when combined with alcohol.

(continued on next page)

**Table 1 (continued)**

Structure and name of drug	Remarks
	
	Oseltamivir specially developed for influenza virus. It inhibits Nucleoside Transporter Enzyme (inhibits Exocytosis) Side effects: Irregular heart beat, arm pain etc.

### 3.2. Vaccines to control the Covid-19

There are mainly four types of vaccines to control Covid-19 as given below.

- (i) RNA Vaccines: This vaccine uses a copy of mRNA and produces an immune response.
- (ii) Adenovirus vector vaccines: These are non replicating viral vector vaccine, it presents antigen which elicits a systemic immune response.
- (iii) Inactivated virus vaccines: These consist of viral particles (killed by heat or formaldehyde to lose disease-producing capacity while still stimulating an immune response)
- (iv) Subunit vaccines: These present one or more antigens, and antigens involved are often protein subunits but can be any molecule that is a fragment of the virus.

Except above four types of vaccines, other types of vaccines that are in chemical trial are virus-like particle vaccine, DNA plasmid vaccines, lentivirus vector vaccine, conjugate vaccines and vesicular stomatitis virus. There are 14 vaccines authorized by regulatory authorities and belong to mainly the above four types. A description of each vaccine is given in [Table 2](#).

### 4. Green approaches to counter viral infections

#### 4.1. Review of literature on the antiviral activity of natural extracts

The commonly used allopathic medicines or so-called modern medicines have found significant praise because of their fast action and potency. However, their continuous usage can cause a patient to develop immunity against the same. In addition, these drugs have also been known to cause several side effects, despite being too expensive [4–6]. On the other hand, the medicines having natural origin although have been criticized for having slower action; still, most of these have almost negligible side effects [7,8]. The medicinal plants and herbs contain bioactive metabolites that have pharmacological properties. Therefore, these alternatives present a natural source of cheaply available drugs having less harmful effects [38]. The plant products have antioxidant activities due to the presence of phenolic compounds. These compounds have potential antimicrobial activity, thereby imparting excellent medicinal properties to plant-based drug products. The different antiviral mechanisms of the plant-based medicines have been identified against some of the notable viral pathogens, including the coronavirus, coxsackievirus, dengue virus, enterovirus, herpes virus, influenza virus, measles virus, etc. [39,40]. It has also been identified that in which part of the viral life cycle these medicinal products interact with them, e.g.,

entry, replication, release, etc. Several articles are available in the literature on the antibacterial, antifungal, etc., activities of the naturally-derived extracts, etc. Herein we have gathered a collection of literature showing the antiviral activity of the natural extracts derived from various herbs and medicinal plants as detailed vide infra.

Various polyphenols, flavonoids, and alkaloids have been isolated from plants and used as anti-influenza agents [41]. Polyphenol extract derived from *Geranium sanguineum* L. has shown potential anti-viral activity along with antioxidant and radical scavenging capabilities [42]. Bioflavonoid ginkgetin was isolated from *Ginkgo biloba* L. and *Cephaelotaxus harringtonia* K., and have shown significant anti-influenza activity [43,44]. Medicinal plants such as *Bergenia ligulata*, *Nerium indicum*, and *Holoptelia integrifolia* have shown anti-influenza activity [45]. Lignans derived from *Rhinacanthus nasutus* have also exhibited anti-flu activity [46]. *S. alopecuroides* L., *S. flavescent* and *S. subprostrata* (shandougen) contain alkaloids, namely oxymatrine and matrine, and have shown to inhibit viral replication in case of hepatitis C virus [47–51]. *A. nilotica*, *B. carterii*, *E. schimperi*, *Q. infectoria*, *P. cubeba*, *T. ammi*, and *S. aromaticum* have shown effective performance against HCV [52]. Essential oils derived from *Santolina insularis* have shown effective performance against the herpes virus [53]. Several plants have been screened for ethnomedical backgrounds for antiviral activity against the herpes virus without having any toxic effects on cells [54]. *H. integrifolia* and *N. indicum* have shown considerable activity against the herpes virus without showing any significant toxic influence against the cells [45].

The flavonoids have shown considerable antiviral activity. The antiviral activity of the flavanones has been known since 1990s [55]. Apigenin from sweet basil has shown significant activity against adenoviruses and hepatitis B virus [56]. In addition, apigenin has also shown activity towards suppression of protein synthesis in African swine fever virus (ASFV) [57]. The reduction of mature microRNA122 of HCV has been displayed by apigenin [58]. Baicalein and luteolin are other flavones that have been investigated for their antiviral activity. Baicalein considerably reduced the protein synthesis in the human cytomegalovirus (HCMV) and the viral DNA synthesis [59]. It also impaired the replication of avian influenza H5N1 virus in human epithelial cells [60]. Baicalein and baicalin exerted significant antiviral influence against the dengue virus (DENV) while interfering with the various steps of the virus replication [61–63]. Luteolin has shown antiviral activity against HIV-1 reactivation [64]. It also shows significant inhibition activity against Epstein-Barr virus (EBV) reactivation by suppressing the related genes in the early stages [65]. Luteolin or luteolin-rich fractions have also shown considerable antiviral activity against the SARS-CoV, rhesus rotavirus, and Japanese encephalitis virus (JEV) [66–68].

Among the flavonols, the antiviral effect of quercetin has been the most widely investigated. Oral treatment of mice with quercetin

**Table 2**  
List of some of the available vaccines for Covid-19.

Name of Vaccine	Type	Description about Vaccine	Side Effects
Pfizer-BioNTech	RNA vaccine	Its brand name is Comirnaty. It is given by intra muscular injection and vaccination requires two doses with gap of three weeks.	Pain and swelling of injection site, tiredness, headache, muscle ache, chills, joint pain and fever.
Moderna	RNA vaccine	It is used in people aged 18 years and older. It is given by intramuscular injection 0.5 mL dose with gap of four weeks	Pain at injection site, fatigue, headache, myalgia and joint pain.
BBIBP-CorV	Inactivated virus Vaccine	It also known as sinopharm COVID-19 vaccine, given by intramuscular	Fever, fatigue, difficulty in breathing, diarrhea, nausea, cough
CoronaVac	Inactivated virus Vaccine	It is also known as sinovac COVID-19 vaccine. Given by intramuscular and stored at 2–8 °C temperature	Blood pressure increase, Headache, Vaccination site pain, dizziness, rash
Covaxin	Inactivated virus Vaccine	Also known as BBV152. Given by intramuscular	Mild headaches, pain or swelling at the injection site, fever, irritability
WIBP-CorV	Inactivated virus Vaccine	Given by intramuscular	Fever, pain or swelling at injection site, rash
CoviVac	Inactivated virus Vaccine	Given by intramuscular	Pain or swelling at injection site, no other specific side effects.
Sputnik Light	virus vector vaccine	Given by intramuscular	Pain or swelling at injection site, increasing blood pressure, breathing difficulties.
Sputnik V	virus vector vaccine	Given by intramuscular	Breathing difficulties, convulsions, swelling, muscle weakness
Oxford-AstraZeneca	virus vector vaccine	Its brand name is Covishield and Vaxzevria. Given by intramuscular	Vomiting, diarrhea, swelling, redness at injection site, low-level blood platelets.
Convidecia	virus vector vaccine	It's another name is AD5-Ncov. Given by intramuscular and intranasal.	No severe adverse effect
Johnson & Johnson	virus vector vaccine	It is given by Intramuscular	Coughing, joint pain, fever, chills and swelling at injection site.
EpiVacCorona	Protein subunit vaccine	Given by intramuscular	No adverse side effects
RBD-Dimer	Protein subunit vaccine	Given by intramuscular	Mild side effects, injection pain, redness and swelling.

provided protection from the Mengo virus [69,70]. Quercetin, in combination with the murine type I interferon (IFN) provided enhanced protection [71]. Dose-dependent antiviral activity of quercetin was observed against poliovirus type 1, HSV-1, HSV-2, and respiratory syncytial virus (RSV) [72,73]. Quercetin has also shown to reduce the Newcastle disease virus (NDV) replication, vesicular stomatitis virus (VSV) as well as some of the influenza viruses [74]. Computational studies have shown that quercetin can considerably inhibit the neuraminidase of influenza A H1N1 and H7N9 viruses [75,76]. Kaempferol and its several derivatives having acyl functionality have shown

considerable performance against the HCMV [77]. Its derivatives extracted from *Ficus benjamina* leaves have shown effective antiviral behavior against HSV [78].

2-phenyl-3,4-dihydro-2Hchromene skeleton is the characteristic of flavans. Among these, the antiviral activity of the catechins and their derivatives, such as epicatechin, epicatechin gallate, epigallocatechin (EGC), and epigallocatechin gallate (EGCG) have been considerably investigated [79]. The tea catechins have also shown antiviral activity against HIV-1 [80,81]. EGCG and ECG have shown effective action in the inhibition of the HIV-1 reverse transcriptase *in vitro* [82,83]. A significant activity of the tea catechins has also been shown against the herpes viruses [84]. Soybeans and fava beans contain an isoflavonoid named Genistein, which functioning as a tyrosinase inhibitor, reduced bovine serum herpesvirus type 1, and New World arenavirus Pichinde replication [85,86]. It has also been shown to inhibit the HIV infection of the resting CD4 T cells and macrophages [87].

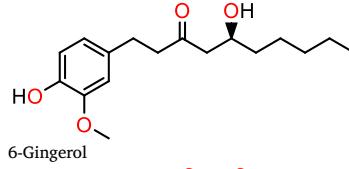
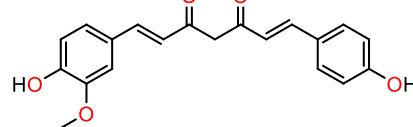
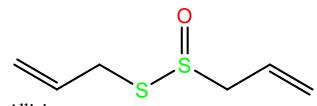
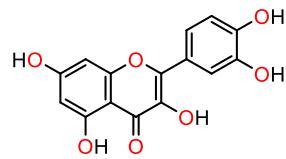
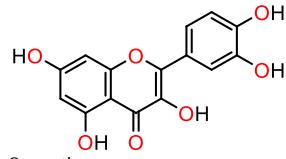
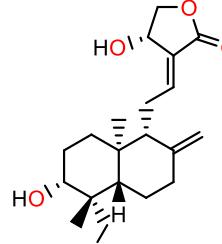
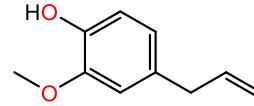
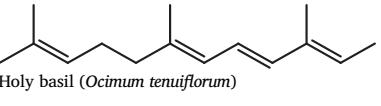
#### 4.2. Innovations in the delivery and bioavailability of phytochemicals

The introduction of organic synthesis from the areas of pharmaceutical chemistry, multicomponent synthesis strategies, nanomaterial preparation, etc., has paved the way towards chemical functionalization of the phytochemical constituents derived from the natural extracts [88]. These innovations have improved the pharmacokinetic and clinical output of the phytochemical-based drug systems. The approaches that have been commonly used as phytosomes, hydrogel formation, nanoscience, microspheres, transferosomes, ethosomes, etc., have improved the delivery of plant-based antiviral agents. Although, here it is important to note that only a few studies are available in the literature on the application of natural extract-based drug delivery systems or so-called herbal drug delivery systems. However, in this section, we have outlined a few of the successful attempts in this area. *Flos Lonicerae Japonicae* and *Fructus Forsythiae* are commonly used Chinese herbal remedies. They have been further chemically modified using a chitosan oligosaccharide to improve the bioavailability and the anti-influenza activity [89]. The oral bioavailability of apigenin was increased by using soybean oil-Tween 80 emulsion system, which was applied on the animal model in addition to the particle size estimation and the zeta potential measurements [90]. The oral absorption of baicalin was improved using a micellar formulation comprising a copolymer and sodium taurocholate [91]. Oleanolic acid solubility was increased using a formulation consisting of 50% ethyl oleate, 35% Cremophor EL, and 15% alcohol. This resulted in a sustained released behavior and improvement in the systemic rat bioavailability [92]. The bioavailability of a herbal drug was improved using honokiol and sulfobutyl ether-β-cyclodextrin. The in-vitro results showed an enhanced release was observed [93]. PLGA (poly (lactic-co-glycolic acid)) was used to develop andrographolide microspheres to improve its oral bioavailability [94].

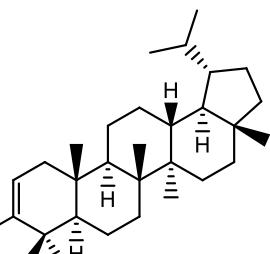
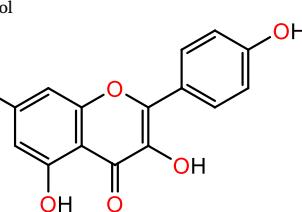
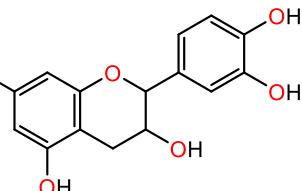
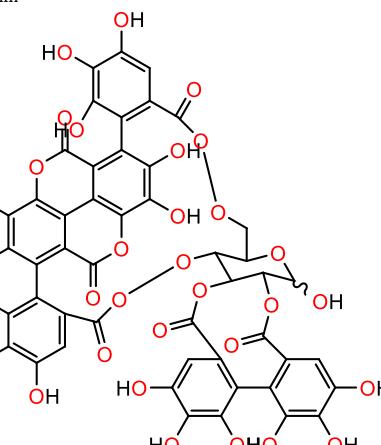
#### 5. Application of phytochemicals in countering the Covid-19

The non-availability of the Covid-19-targeted conventional therapeutics such as vaccines, antibiotics, etc., has led to the use of broad-spectrum antibiotics and well-established antiviral treatments. Herein, the extracts derived from the natural products that are the rich source of the active compounds can be utilized effectively against the coronavirus [95]. Extracts derived from several traditional Chinese medicinal plants have been observed to inhibit the replication of SARS-CoV. Over 200 extracts were investigated in a study, and their potency was established in countering the SARS-CoV [96]. Bioflavonoids derived from *Torreya nucifera* were found to successfully inhibit the replication of SARS-CoV 3CL<sup>pro</sup> [97]. The ethanolic extract derived from the leaves of this plant showed 62% inhibition activity at 100 µg/L concentration. Using the fluorescence resonance energy transfer (FRET) method, eight diterpenoids and four bioflavonoids were identified as potential inhibitors. The experimental results of the enzymatic tests were supported by the

**Table 3**  
Medicinal plants as anti-corona agents.

Drug	Herb	Remarks
 6-Gingerol	 Ginger ( <i>Zingiber officinale</i> )	Strong antiviral, Supports Immune system, reduce risk of diabetes and cancer
 Demethoxy curcumin	 Turmeric ( <i>Curcuma longa</i> )	Strong Antiviral, Anti-Inflammatory, Protect Against Heart Disease, Protect Against Heart Disease
 Allicin	 Garlic ( <i>Allium sativum</i> )	Proteolytic and hemagglutinating activity and stop viral replication, Cold and Flu, Anti-bacterial and Anti-parasitic, Prevention of Heart Disease, Cancer Prevention.
 Quercetin	 Onion ( <i>Allium cepa</i> )	Strong antiviral, Cancer prevention, Skin and hair, Blood pressure moderation.
 Quercetin	 Green Chilli ( <i>Capsicum annum</i> )	Strong antiviral, anti-cancer, anti-inflammatory
 Andrographolide	 Green Chiretta, creat ( <i>Andrographis paniculata</i> )	Antiviral and anti-inflammatory, inhibits the replication of influenza virus, decreases inflammation of lung, prevents the damage of liver cells
 Eugenol	 Holy basil ( <i>Ocimum tenuiflorum</i> )	Anti-Viral
 $\alpha$ -Farnesene		Inhibitory action towards HCoV-NL63 (continued on next page)

**Table 3 (continued)**

Drug	Herb	Remarks
Lupenol	 Chinese Rain Bell ( <i>Strobilanthes cusia</i> )	
Kaempferol	 Spinach ( <i>Spinacia oleracea</i> )	Antiviral properties
Catechin	 Kamelija Kineska ( <i>Camellia Sinensis(L.) kuntze</i> )	Strong antiviral properties
Punicalagin	 Pomegranate ( <i>Punica granatum</i> )	Strong antiviral properties

molecular docking analysis [97]. The extracts from *Houttuynia cordata* Thunb. containing quercetin, quercitrin and cyanserine was assessed for the antiviral activity in the coronavirus and dengue virus infections in mice via the *in vitro* tests [98]. These flavonoids were evaluated for their efficacy against the mouse coronavirus and dengue virus in the virus neutralization tests and acute oral toxicity in the mice. The IC<sub>50</sub> of the extracts was 0.98 mg/mL and 7.50 mg/mL for coronavirus and the dengue virus, respectively. Up to 2000 mg/kg oral doses fed to the mice did not produce any acute toxicity. Furthermore, a synergistic activity of quercetin and quercitrin was observed in the antiviral activity [98]. Against the MERS-CoV-3 coronavirus, the potential activity of flavonoids was characterized [99]. The compounds, namely herbacetin, isobavachalcone, quercetin 3-β-d-glucoside, and helichristetine, were found to successfully block the enzymatic activity of the MERS-CoV-3 coronavirus. Flavonoids having hydrophobic or carbohydrate groups were used as inhibitors against the MERS-CoV 3CL<sup>pro</sup> [99]. Flavonoids were also investigated by Nguyen et al. against *Pichia pastoris* with the acute respiratory syndrome (SARS-CoV) [100]. The synthesis and antiviral action

of some quercetin derivatives were evaluated against SARS-associated coronavirus (SCV) and hepatitis C virus (HCV) [101]. The structure-activity studies of the quercetin-3-β-galactoside and its derivatives were evaluated against the SARS-CoV 3CL<sup>pro</sup> using the structure-activity relationships [102]. The quercetin-3-β-galactoside had the potential as an anti-SARS drug and helped in the elucidation of the mechanism of inhibition against the targeted enzyme. The *Sambucus Formosana Nakai* extract provided excellent anti-HCoV-NL63 potential by the activity of the phenolic acid components that included the coffee acid, chlorogenic acid, and gallic acid [103]. The polyphenolic components present in the green tea have been shown to provide antiviral effect [104]. The leaf extracts of *Toona sinensis Roem* provided inhibition activity to SARS-CoV [105]. The flavonoids existing in *Galla chinensis* or *Veronica linrifolia* extracts have shown the binding capability to the surface spiky proteins of the SARS virus preventing it's penetration to the cell [106]. The experimental studies were supported by the molecular docking analysis. The aqueous extracts of the *Isatis indigotica* root contain several phenolic compounds and have shown anti-SARS-CoV 3CL<sup>pro</sup>

[107]. Some of the medicinal plants and their phytochemical constituents that could be potential antiviral agents are listed in Table 3.

Yi et al. studied the influence of the phytochemical components of flavonoids and polyphenols on the entry of SARS-CoV [68]. Reserpine and Aescin showed the interference to block the entry of the virus inside the cells and have shown the inhibition of the activity of the 3CLpro enzyme of the virus [108]. Lectins isolated from different plants have shown a considerable anti-SARS-CoV activity [109]. Emodin has shown the inhibition of the 3a ion channel of coronavirus and has shown to inhibit the release of the SARS-CoV from the infected cells [110]. Griffithsin, the protein extracted from the red algae *Griffithsia*, has been shown to be effective against the MERS-CoV [111]. Here it is noteworthy to mention that the Griffithsin has a high specificity index towards the human coronavirus [112], which suggests its high applicability in clinical trials as well as usage in animal model studies. Saikosaponins (A, B2, C, and D) that are derived from plants displayed good to moderate antiviral potential against HCoV-229E [113]. The methanolic extract of the leaves of *Strobilanthes cusia* has shown an effective reduction in the virus in the infected cells [114]. Tryptanthrin is a naturally occurring alkaloid having the basic indoloquinazoline moiety that exhibited high antiviral activity against HCoV [115]. The tryptanthrin has also been shown to inhibit the early and late replication periods of HCoV-NL63 [116]. Silvestrol was investigated in an ex vivo study of the bronchial epithelial cells to the inhibition of RNA helicase eIF4A [117]. Qingfei Paidu Decoction (QFPD) consisted of a total of 21 components, including the herbs and mineral drugs, and produced an effectiveness of 92% among the patients at all the stages, including the cured and the discharged, wherein the clinical symptoms disappeared, and patients showed stability and improvement [118].

A fruitful approach in developing an understanding of the performance of a natural product is the use of bioinformatics studies. The computational analysis has shown considerable support in the identification of the best available drug candidates. Besides, the computational studies have also shown their application in the exploration of the genetic pathways of the antiviral metabolites of natural products. The computational modeling studies have also allowed the virtual screening of the SARS-CoV-2 inhibitors. The bioinformatics approach plays a crucial role in identifying the potential antagonistic compounds that can target the binding sites of the SARS-CoV viral proteins via complex molecular interactions for viral attachment and replication [119,120]. The computational assistance has led to a rise in the pace of the research and development ongoing in the exploration of the SARS-CoV-2 solutions. The design and the synthesis of the novel compounds that can play an important role against the Covid-19 can be facilitated using computational studies. The correlation of the structural features of the novel inhibitory compounds with their inhibition potency can be characterized using molecular docking studies [75,76,121]. The molecular dynamics simulation is a viable tool in this context. Earlier, these studies have shown the screening of the binding affinity of several flavonoids by identifying the role of the different functional groups that take part in the interaction. In addition, several databases have been available such as the National Center for Biotechnology Information (NCBI), and Kyoto Encyclopedia of Genes and Genomes (KEGG), The Arabidopsis Information Resource (TAIR), Medicinal Plant Database for Drug Designing (MPD3), and the International Ethnobotany Database (ebDB). These databases have provided specific and useful information of medicinal plants and their metabolic pathways. It is important to note that some of these are non-commercial repositories and even provide free of cost information regarding the strong structure and data export features. In some cases, comprehensive information about the detailed structure and potential activities of the phytochemicals are also available.

## 6. Conclusions and prospects

The Covid-19 pandemic is an unprecedented event in the course of history. It has led to a huge loss of human life and has produced a large-scale economic and sociological impact all over the world in different sections such as healthcare, business, education, sports, entertainment, travel, and tourism, etc. Since the onset of the pandemic, there has been research and development in the area of cure as well as prevention in the form of medicines and vaccinations; however, in most cases, not much promise has been observed. Although recently, fortunately, few medicines and vaccination treatments have been coming across, still, there are cost factors associated which restrict the easy availability of these solutions to the target public. Furthermore, the use of modern medicine has been often criticized due to the associated side effects.

In this case, the prime objective of this review article is to provide an overview of some of the antiviral medicines based on the plant products that have produced significant performance. The naturally derived bioactive compounds function as antioxidants, direct enzyme inhibitors, and block the surface protein receptors in the virus. A variety of medicinal plants have been shown to have a considerable source of phytochemicals and have exhibited a wide range of bioactivity. Therefore, it is proposed herein that these drugs could provide useful alternatives compared to the modern medical treatment of the Covid-19. The research articles collected in this review show that the medicinal plants exhibit promising therapeutic potential, especially against viral infections, which is the focus of the present review. Some concerns have been raised against the reaching of the plant-based medicines to the target virus. In this context, the development in the area of nanoscience and drug delivery systems has shown promising progress. Although there are numerous systems available on modern drug-delivery technologies, however, this area is still currently at the growing stage in the context of herbal medicines, and much progress has to be achieved. The phytochemical-based components discussed herein have provided hope that the Covid-19 pandemic can be tackled based on the Green Chemistry-based approaches that can afford an effective solution as well as an environmentally sustainable health care practice.

## Disclaimer

The authors alone are responsible for the content and writing of the paper.

## Author contributions

Dr. DS Chauhan and Dr. S Yadav drafted the manuscript and prepared the Figures and Tables. Prof. MA Quraishi did the data analysis and critical revision.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

- [1] K. Yuki, M. Fujiogi, S. Koutsogiannaki, COVID-19 Pathophysiology: A Review, *Clinical Immunology*, 2020, p. 108427.

- [2] S. Salehi, A. Abedi, S. Balakrishnan, A. Gholamrezanezhad, Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients, *Am. J. Roentgenol.* (2020) 1–7.
- [3] E. De Clercq, G. Li, Approved antiviral drugs over the past 50 years, *Clin. Microbiol. Rev.* 29 (2016) 695–747.
- [4] D. Bennadi, Self-medication: a current challenge, *J. Basic Clin. Pharm.* 5 (2013) 19.
- [5] F. Attena, Limitations of western medicine and models of integration between medical systems, *J. Alternative Compl. Med.* 22 (2016) 343–348.
- [6] S.R. Gawde, Y.C. Shetty, D.B. Pawar, Knowledge, attitude, and practices toward ayurvedic medicine use among allopathic resident doctors: a cross-sectional study at a tertiary care hospital in India, *Perspectives in Clinical Research* 4 (2013) 175.
- [7] C.A. Newall, L.A. Anderson, J.D. Phillipson, *Herbal Medicines. A Guide for Health-Care Professionals*, The pharmaceutical press, 1996.
- [8] S. Verma, S.J.V.W. Singh, Current and future status of herbal medicines 1 (2008) 347.
- [9] C. Bailly, G. Vergoten, Glycyrrhizin: an alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome? *Journal of Pharmacology and Therapeutics* (2020) 107618.
- [10] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, Remdesivir for the Treatment of Covid-19, *New England Journal of Medicine*, 2020.
- [11] Q. Cai, M. Yang, D. Liu, J. Chen, D. Shu, J. Xia, X. Liao, Y. Gu, Q. Cai, Y. Yang, Experimental treatment with favipiravir for COVID-19: an open-label control study, *Engineering* (2020).
- [12] J. Chen, L. Xia, L. Liu, Q. Xu, Y. Ling, D. Huang, W. Huang, S. Song, S. Xu, Y. Shen, Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19, in: *Open Forum Infectious Diseases*, Oxford University Press US, 2020, p. ofaa241.
- [13] Z. Sahraei, M. Shabani, S. Shokouhi, A. Saffaei, Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine, *Int. J. Antimicrob. Agents* (2020) 105945.
- [14] F. Touret, X. de Lamballerie, Of Chloroquine and COVID-19, *Antiviral Research*, 2020, p. 104762.
- [15] A.S. Evans, *Viral Infections of Humans: Epidemiology and Control*, Springer Science & Business Media, 2013.
- [16] J. Lessler, N.G. Reich, R. Brookmeyer, T.M. Perl, K.E. Nelson, D.A. Cummings, Incubation periods of acute respiratory viral infections: a systematic review, *Lancet Infect. Dis.* 9 (2009) 291–300.
- [17] J.M. Walter, R.G. Wunderink, Severe respiratory viral infections: new evidence and changing paradigms, *Infectious Disease Clinics* 31 (2017) 455–474.
- [18] L.L. Poon, D.K. Chu, K.-H. Chan, O.K. Wong, T.M. Ellis, Y. Leung, S.K. Lau, P. Woo, K. Suen, K. Yuen, Identification of a novel coronavirus in bats, *J. Virol.* 79 (2005) 2001–2009.
- [19] Z.A. Memish, N. Mishra, K.J. Olival, S.F. Fagbo, V. Kapoor, J.H. Epstein, R. AlHakeem, A. Durosinaloun, M. Al Asmary, A. Islam, Middle East respiratory syndrome coronavirus in bats, Saudi Arabia, *Emerg. Infect. Dis.* 19 (2013) 1819.
- [20] V.M. Corman, D. Muth, D. Niemeyer, C. Drosten, Hosts and sources of endemic human coronaviruses, in: *Advances in Virus Research*, Elsevier, 2018, pp. 163–188.
- [21] B.S. Chhikara, B. Rathi, J. Singh, F.N.U. Poonam, Corona virus SARS-CoV-2 disease COVID-19: infection, prevention and clinical advances of the prospective chemical drug therapeutics, *Chemical Biology Letters* 7 (2020) 63–72.
- [22] P.K. Rai, Z. Usmani, V.K. Thakur, V.K. Gupta, Y.K. Mishra, Tackling COVID-19 pandemic through nanocoatings: confront and exactitude, *Current Research in Green and Sustainable Chemistry* 3 (2020) 100011.
- [23] Y. Wan, J. Shang, R. Graham, R.S. Baric, F. Li, Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus, *J. Virol.* 94 (2020).
- [24] M.A. Shereen, S. Khan, A. Kazmi, N. Bashir, R. Siddique, COVID-19 infection: origin, transmission, and characteristics of human coronaviruses, *J. Adv. Res.* 24 (2020) 91–98.
- [25] Y. Shi, Y. Wang, C. Shao, J. Huang, J. Gan, X. Huang, E. Bucci, M. Piacentini, G. Ippolito, G. Melino, COVID-19 infection: the perspectives on immune responses, in: *Nature Publishing Group*, 2020.
- [26] W. McKibbin, R. Fernando, The economic impact of COVID-19, *Economics in the Time of COVID-19* (2020) 45.
- [27] M. Maliszewska, A. Mattoo, D. Van Der Mensbrugge, The Potential Impact of COVID-19 on GDP and Trade: A Preliminary Assessment, The World Bank, 2020.
- [28] S. Burgess, H.H. Sievertsen, Schools, skills, and learning: the impact of COVID-19 on education, *VoxEu.org* (2020) 1.
- [29] A. Cortegiani, G. Ingoglia, M. Ippolito, A. Giarratano, S. Einav, A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19, *J. Crit. Care* 57 (2020) 279–283.
- [30] J. Chen, D. Liu, L. Liu, P. Liu, Q. Xu, L. Xia, Y. Ling, D. Huang, S. Song, D. Zhang, A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19), *J. Zhejiang Univ.* 49 (2020) 215–219.
- [31] D. Huang, H. Yu, T. Wang, H. Yang, R. Yao, Z. Liang, Efficacy and safety of umifenovir for coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis, *J. Med. Virol.* (2020).
- [32] B. Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19, *N. Engl. J. Med.* 382 (2020) 1787–1799.
- [33] J. Lim, S. Jeon, H.-Y. Shin, M.J. Kim, Y.M. Seong, W.J. Lee, K.-W. Choe, Y.M. Kang, B. Lee, S.-J. Park, Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR, *J. Kor. Med. Sci.* 35 (2020) e79.
- [34] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, Remdesivir for the treatment of Covid-19—preliminary report, *N. Engl. J. Med.* (2020).
- [35] J.S. Khalili, H. Zhu, N.S.A. Mak, Y. Yan, Y. Zhu, Novel coronavirus treatment with ribavirin: groundwork for an evaluation concerning COVID-19, *J. Med. Virol.* 92 (2020) 740–746.
- [36] L. Dong, S. Hu, J. Gao, Discovering drugs to treat coronavirus disease 2019 (COVID-19), *Drug Discoveries and Therapeutics* 14 (2020) 58–60.
- [37] Q. Tan, L. Duan, Y. Ma, F. Wu, Q. Huang, K. Mao, W. Xiao, H. Xia, S. Zhang, E. Zhou, Is oseltamivir suitable for fighting against COVID-19: *in silico* assessment, *in vitro* and retrospective study, *Bioorg. Chem.* 104 (2020) 104257.
- [38] R. Naithani, L.C. Huma, L.E. Holland, D. Shukla, D.L. McCormick, R.G. Mehta, R.M. Moriarty, Antiviral activity of phytochemicals: a comprehensive review, *Mini Rev. Med. Chem.* 8 (2008) 1106–1133.
- [39] L.-T. Lin, W.-C. Hsu, C.-C. Lin, Antiviral natural products and herbal medicines, *Journal of Traditional and Complementary Medicine* 4 (2014) 24–35.
- [40] K. Kitazato, Y. Wang, N. Kobayashi, Viral infectious disease and natural products with antiviral activity, *Drug Discoveries & Therapeutics* 1 (2007) 14–22.
- [41] X. Wang, W. Jia, A. Zhao, X. Wang, Anti-influenza agents from plants and traditional Chinese medicine, *Phytother. Res.* 20 (2006) 335–341.
- [42] M. Sokmen, M. Angelova, E. Krumova, S. Pashova, S. Ivacheva, A. Sokmen, J. Serkedjieva, *In vitro* antioxidant activity of polyphenol extracts with antiviral properties from Geranium sanguineum L., *Life Sci.* 76 (2005) 2981–2993.
- [43] K. Miki, T. Nagai, K. Suzuki, R. Tsujimura, K. Koyama, K. Kinoshita, K. Furuhata, H. Yamada, K. Takahashi, Anti-influenza virus activity of biflavonoids, *Bioorg. Med. Chem. Lett* 17 (2007) 772–775.
- [44] T. Nagai, Y. Miyachi, T. Tomimori, Y. Suzuki, H. Yamada, *In vivo* anti-influenza virus activity of plant flavonoids possessing inhibitory activity for influenza virus sialidase, *Antivir. Res.* 19 (1992) 207–217.
- [45] M. Rajbhandari, U. Wegner, M. Jülich, T. Schoepke, R. Mentel, Screening of Nepalese medicinal plants for antiviral activity, *J. Ethnopharmacol.* 74 (2001) 251–255.
- [46] M.R. Kernan, A. Sendi, J.L. Chen, S.D. Jolad, P. Blanc, J.T. Murphy, C.A. Stoddart, W. Nanakorn, M.J. Balick, E. Rozhon, Two new lignans with activity against influenza virus from the medicinal plant Rhinacanthus nasutus, *J. Nat. Prod.* 60 (1997) 635–637.
- [47] J. Liu, M. Zhu, R. Shi, M. Yang, *Radix Sophorae flavescentis* for chronic hepatitis B: a systematic review of randomized trials, *Am. J. Chin. Med.* 31 (2003) 337–354.
- [48] L.-G. Lu, M.-D. Zeng, Y.-M. Mao, J.-Q. Li, M.-B. Wan, C.-Z. Li, C.-W. Chen, Q.-C. Fu, J.-Y. Wang, W.-M. She, Oxymatrine therapy for chronic hepatitis B: a randomized double-blind and placebo-controlled multi-center trial, *World J. Gastroenterol.* 9 (2003) 2480.
- [49] L.-G. Lu, M.-D. Zeng, Y.-M. Mao, J.-Y. Fang, Y.-L. Song, Z.-H. Shen, A.-P.J.W.j.o.g. Cao, Inhibitory effect of oxymatrine on serum hepatitis B virus DNA in HBV transgenic mice, *World J. Gastroenterol.* 10 (2004) 1176.
- [50] Y.Y. Yu, Q.H. Wang, L.M. Zhu, Q.B. Zhang, D.Z. Xu, Y.B. Guo, C.Q. Wang, S.H. Guo, X.Q. Zhou, L.X. Zhang, A clinical research on oxymatrine for the treatment of chronic hepatitis B, *Chin. J. Hepatol.* 10 (2002) 280–281.
- [51] Y.-M. Mao, M.-D. Zeng, L.-G. Lu, M.-B. Wan, C.-Z. Li, C.-W. Chen, Q.-C. Fu, J.-Y. Wang, W.-M. She, X. Cai, Capsule oxymatrine in treatment of hepatic fibrosis due to chronic viral hepatitis: a randomized, double blind, placebo-controlled, multicenter clinical study, *World J. Gastroenterol.: WJG* 10 (2004) 3269.
- [52] G. Hussein, H. Miyashiro, N. Nakamura, M. Hattori, N. Kakiuchi, K. Shimotohno, Inhibitory effects of Sudanese medicinal plant extracts on hepatitis C virus (HCV) protease, *Phytother. Res.* 14 (2000) 510–516.
- [53] A. De Logu, G. Loy, M.L. Pellerano, L. Bonsignore, M.L. Schivo, Inactivation of HSV-1 and HSV-2 and prevention of cell-to-cell virus spread by *Santolina insularis* essential oil, *Antivir. Res.* 48 (2000) 177–185.
- [54] P. Vijayan, C. Raghu, G. Ashok, S. Dhanaraj, B. Suresh, Antiviral activity of medicinal plants of Nilgiris, *Indian J. Med. Res.* 120 (2004) 24–29.
- [55] I. Muci, Z. Gyulai, I. Beladi, Combined effects of flavonoids and acyclovir against herpesviruses in cell cultures, *Acta Microbiol. Hung.* 39 (1992) 137.
- [56] L.C. Chiang, L.T. Ng, P.W. Cheng, W. Chiang, C.C. Lin, Antiviral activities of extracts and selected pure constituents of *Ocimum basilicum*, *Clin. Exp. Pharmacol. Physiol.* 32 (2005) 811–816.
- [57] A. Hakobyan, E. Arabyan, A. Avetisyan, L. Abroyan, L. Hakobyan, H. Zakaryan, Apigenin inhibits African swine fever virus infection *in vitro*, *Arch. Virol.* 161 (2016) 3445–3453.
- [58] C. Shibata, M. Ohno, M. Otsuka, T. Kishikawa, K. Goto, R. Muroyama, N. Kato, T. Yoshikawa, A. Takata, K. Koike, The flavonoid apigenin inhibits hepatitis C virus replication by decreasing mature microRNA122 levels, *Virology* 462 (2014) 42–48.
- [59] D.L. Evers, C.-F. Chao, X. Wang, Z. Zhang, S.-M. Huong, E.-S. Huang, Human cytomegalovirus-inhibitory flavonoids: studies on antiviral activity and mechanism of action, *Antivir. Res.* 68 (2005) 124–134.
- [60] P. Sithisarn, M. Michaelis, M. Schubert-Zsilavecz, J. Cinatl Jr., Differential antiviral and anti-inflammatory mechanisms of the flavonoids biochanin A and baicalein in H5N1 influenza A virus-infected cells, *Antivir. Res.* 97 (2013) 41–48.
- [61] E. Moghaddam, B.-T. Teoh, S.-S. Sam, R. Lani, P. Hassandarvish, Z. Chik, A. Yueh, S. Abubakar, K. Zandi, Baicalin, a metabolite of baicalein with antiviral activity against dengue virus, *Sci. Rep.* 4 (2014) 5452.
- [62] K. Zandi, T.-H. Lim, N.-A. Rahim, M.-H. Shu, B.-T. Teoh, S.-S. Sam, M.-B. Danlami, K.-K. Tan, S. Abubakar, Extract of *Scutellaria baicalensis* inhibits dengue virus replication, *BMC Compl. Alternative Med.* 13 (2013) 91.

- [63] K. Zandi, B.-T. Teoh, S.-S. Sam, P.-F. Wong, M.R. Mustafa, S. AbuBakar, Novel antiviral activity of baicalein against dengue virus, *BMC Compl. Alternative Med.* 12 (2012) 1–9.
- [64] R. Mehta, S. Bivalkar-Mehla, A. Chauhan, A flavonoid, luteolin, cripples HIV-1 by abrogation of tat function, *PLoS One* 6 (2011), e27915.
- [65] G. Williamson, M.N. Clifford, Colonic metabolites of berry polyphenols: the missing link to biological activity? *Br. J. Nutr.* 104 (2010) S48–S66.
- [66] W. Fan, S. Qian, P. Qian, X. Li, Antiviral activity of luteolin against Japanese encephalitis virus, *Viral Research* 220 (2016) 112–116.
- [67] K. Knipping, J. Garssen, B. van't Land, An evaluation of the inhibitory effects against rotavirus infection of edible plant extracts, *Virol. J.* 9 (2012) 1–8.
- [68] L. Yi, Z. Li, K. Yuan, X. Qu, J. Chen, G. Wang, H. Zhang, H. Luo, L. Zhu, P. Jiang, Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells, *J. Virol.* 78 (2004) 11334–11339.
- [69] J. Gütterm, A. Veckenstedt, H. Heinecke, R. Puszta, Effect of quercetin on the course of mengo virus infection in immunodeficient and normal mice. A histologic study, *Acta Virol.* 26 (1982) 148–155.
- [70] A.A. Dayem, H.Y. Choi, Y.B. Kim, S.-G.J.P.O. Cho, Antiviral effect of methylated flavonol isorhamnetin against influenza, *PLoS One* 10 (2015), e0121610.
- [71] A. Veckenstedt, J. Gütterm, I. Bélaïdi, Synergistic action of quercetin and murine alpha/beta interferon in the treatment of Mengo virus infection in mice, *Antivir. Res.* 7 (1987) 169–178.
- [72] B.K. Kang, J.S. Lee, S.K. Chon, S.Y. Jeong, S.H. Yuk, G. Khang, H.B. Lee, S.H. Cho, Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs, *Int. J. Pharm.* 274 (2004) 65–73.
- [73] S.-Y. Lyu, J.-Y. Rhim, W.-B. Park, Antitherapeutic activities of flavonoids against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro, *Arch Pharm. Res. (Seoul)* 28 (2005) 1293–1301.
- [74] W.-K. Cho, P. Weeratunga, B.-H. Lee, J.-S. Park, C.-J. Kim, J.Y. Ma, J.-S. Lee, Epimedium koreanum Nakai displays broad spectrum of antiviral activity in vitro and in vivo by inducing cellular antiviral state, *Viruses* 7 (2015) 352–377.
- [75] Z. Liu, J. Zhao, W. Li, L. Shen, S. Huang, J. Tang, J. Duan, F. Fang, Y. Huang, H. Chang, Computational screen and experimental validation of anti-influenza effects of quercetin and chlorogenic acid from traditional Chinese medicine, *Sci. Rep.* 6 (2016) 19095.
- [76] Z. Liu, J. Zhao, W. Li, X. Wang, J. Xu, J. Xie, K. Tao, L. Shen, R. Zhang, Molecular docking of potential inhibitors for influenza H7N9, *Computational and Mathematical Methods in Medicine*, 2015 (2015). Article ID 480764.
- [77] D. Mitrocota, S. Mitaku, S. Axarlis, C. Harvala, M. Malamas, Evaluation of the antiviral activity of kaempferol and its glycosides against human cytomegalovirus, *Planta Med.* 66 (2000) 377–379.
- [78] L. Yarmolinsky, M. Huleihel, M. Zaccai, S. Ben-Shabat, Potent antiviral flavone glycosides from *Ficus benjamina* leaves, *Fitoterapia* 83 (2012) 362–367.
- [79] J.M. Song, B.L. Seong, Tea catechins as a potential alternative anti-infectious agent, *Expert Rev. Anti-infect. Ther.* 5 (2007) 497–506.
- [80] K. Kawai, N.H. Tsuno, J. Kitayama, Y. Okaji, K. Yazawa, M. Asakage, N. Hori, T. Watanabe, K. Takahashi, H.J.J.o.A. Nagawa, C. Immunology, Epigallocatechin gallate, the main component of tea polyphenol, binds to CD4 and interferes with gp120 binding, *J. Allergy Clin. Immunol.* 112 (2003) 951–957.
- [81] M.P. Williamson, T.G. McCormick, C.L. Nance, W.T. Shearer, Epigallocatechin gallate, the main polyphenol in green tea, binds to the T-cell receptor, CD4: potential for HIV-1 therapy, *J. Allergy Clin. Immunol.* 118 (2006) 1369–1374.
- [82] H. Nakane, K. Ono, Differential inhibition of HIV-reverse transcriptase and various DNA and RNA polymerases by some catechin derivatives, in: *Nucleic Acids Symposium Series*, 1989, p. 115.
- [83] H. Nakane, K. Ono, Differential inhibitory effects of some catechin derivatives on the activities of human immunodeficiency virus reverse transcriptase and cellular deoxyribonucleic and ribonucleic acid polymerases, *Biochemistry* 29 (1990) 2841–2845.
- [84] L.-K. Chang, T.-T. Wei, Y.-F. Chiu, C.-P. Tung, J.-Y. Chuang, S.-K. Hung, C. Li, S.-T. Liu, Inhibition of Epstein–Barr virus lytic cycle by (–)-epigallocatechin gallate, *Biochem. Biophys. Res. Commun.* 301 (2003) 1062–1068.
- [85] S.M. Akula, D.J. Hurley, R.L. Wixon, C. Wang, C.C. Chase, Effect of genistein on replication of bovine herpesvirus type 1, *Am. J. Vet. Res.* 63 (2002) 1124–1128.
- [86] E.M. Vela, G.C. Bowick, N.K. Herzog, J.F. Aronson, Genistein treatment of cells inhibits arenavirus infection, *Antivir. Res.* 77 (2008) 153–156.
- [87] J. Guo, X. Xu, T.K. Rasheed, A. Yoder, D. Yu, H. Liang, F. Yi, T. Hawley, T. Jin, B.J.R. Ling, Genistein interferes with SDF-1-and HIV-mediated actin dynamics and inhibits HIV infection of resting CD4 T cells, *Retrovirology* 10 (2013) 62.
- [88] S. Ben-Shabat, L. Yarmolinsky, D. Porat, A. Dahan, Antiviral effect of phytochemicals from medicinal plants: applications and drug delivery strategies, *Drug Delivery and Translational Research* 10 (2020) 354–367.
- [89] W. Zhou, A. Yin, J. Shan, S. Wang, B. Cai, L. Di, Study on the rationality for antiviral activity of *Flos Lonicerae Japonicae–Fructus Forsythiae* herb couple preparations improved by chito-oligosaccharide via integral pharmacokinetics, *Molecules* 22 (2017) 654.
- [90] B.-K. Kim, A.-R. Cho, D.-J. Park, Enhancing oral bioavailability using preparations of apigenin-loaded W/O/W emulsions: in vitro and in vivo evaluations, *Food Chem.* 206 (2016) 85–91.
- [91] H. Zhang, X. Yang, L. Zhao, Y. Jiao, J. Liu, G. Zhai, In vitro and in vivo study of Baicalin-loaded mixed micelles for oral delivery, *Drug Deliv.* 23 (2016) 1933–1939.
- [92] R. Yang, X. Huang, J. Dou, G. Zhai, L. Su, Self-microemulsifying drug delivery system for improved oral bioavailability of oleanolic acid: design and evaluation, *Int. J. Nanomed.* 8 (2013) 2917.
- [93] C. Xu, Y. Tang, W. Hu, R. Tian, Y. Jia, P. Deng, L. Zhang, Investigation of inclusion complex of honokiol with sulfobutyl ether- $\beta$ -cyclodextrin, *Carbohydr. Polym.* 113 (2014) 9–15.
- [94] Y. Jiang, F. Wang, H. Xu, H. Liu, Q. Meng, W. Liu, Development of andrographolide loaded PLGA microspheres: optimization, characterization and in vitro–in vivo correlation, *International Journal of Phamaceutics* 475 (2014) 475–484.
- [95] K. Chojnicka, A. Witek-Krowiak, D. Skrzypczak, K. Mikula, P. Mlynarz, Phytochemicals containing biologically active polyphenols as an effective agent against Covid-19-inducing coronavirus, *Journal of Functional Foods* 73 (2020) 104146.
- [96] C.-C. Wen, L.-F. Shyur, J.-T. Jan, P.-H. Liang, C.-J. Kuo, P. Arulselvan, J.-B. Wu, S.-C. Kuo, N.-S. Yang, Traditional Chinese medicine herbal extracts of *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, and *Taxillus chinensis* inhibit SARS-CoV replication, *Journal of Traditional and Complementary Medicine* 1 (2011) 41–50.
- [97] Y.B. Ryu, H.J. Jeong, J.H. Kim, Y.M. Kim, J.-Y. Park, D. Kim, T.T.H. Naguyen, S.-J. Park, J.S. Chang, K.H. Park, Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CLpro inhibition, *Bioorg. Med. Chem.* 18 (2010) 7940–7947.
- [98] K. Chiow, M. Phoon, T. Putti, B.K. Tan, V.T. Chow, Evaluation of antiviral activities of *Houttuynia cordata* Thunb. extract, quercetin, quercetin and cinanserin on murine coronavirus and dengue virus infection, *Asian Pacific Journal of Tropical Medicine* 9 (2016) 1–7.
- [99] S. Jo, H. Kim, S. Kim, D.H. Shin, M.S. Kim, Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors, *Chem. Biol. Drug Des.* 94 (2019) 2023–2030.
- [100] T.T.H. Nguyen, H.-J. Woo, H.-K. Kang, Y.-M. Kim, D.-W. Kim, S.-A. Ahn, Y. Xia, D. Kim, Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in *Pichia pastoris*, *Biotechnol. Lett.* 34 (2012) 831–838.
- [101] H.R. Park, H. Yoon, M.K. Kim, S.D. Lee, Y. Chong, Synthesis and antiviral evaluation of 7-O-arylmethylquercetin derivatives against SARS-associated coronavirus (SCV) and hepatitis C virus (HCV), *Arch Pharm. Res. (Seoul)* 35 (2012) 77–85.
- [102] L. Chen, J. Li, C. Luo, H. Liu, W. Xu, G. Chen, O.W. Liew, W. Zhu, C.M. Puah, X. Shen, Binding interaction of quercetin-3- $\beta$ -galactoside and its synthetic derivatives with SARS-CoV 3CLpro: structure–activity relationship studies reveal salient pharmacophore features, *Bioorg. Med. Chem.* 14 (2006) 8295–8306.
- [103] J.-R. Weng, C.-S. Lin, H.-C. Lai, Y.-P. Lin, C.-Y. Wang, Y.-C. Tsai, K.-C. Wu, S.-H. Huang, C.-W. Lin, Antiviral activity of *Sambucus Formosana*Nakai ethanol extract and related phenolic acid constituents against human coronavirus NL63, *Virus Res.* 273 (2019) 197767.
- [104] M.S. Mahmood, J.L. Martínez, A. Aslam, A. Rafique, R. Vinet, C. Laurido, I. Hussain, R.Z. Abbas, A. Khan, S. Ali, Antiviral effects of green tea (*Camellia sinensis*) against pathogenic viruses in human and animals (a mini-review), *Afr. J. Tradit., Complementary Altern. Med.* 13 (2016) 176–184.
- [105] C.-J. Chen, M. Michaelis, H.-K. Hsu, C.-C. Tsai, K.D. Yang, Y.-C. Wu, J. Cinatl Jr., H.W. Doerr, *Toona sinensis* Roem tender leaf extract inhibits SARS coronavirus replication, *J. Ethnopharmacol.* 120 (2008) 108–111.
- [106] X. Wang, Z. Liu, Prevention and treatment of viral respiratory infections by traditional Chinese herbs, *Chinese Med J* 127 (2014) 1344–1350.
- [107] C.-W. Lin, F.-J. Tsai, C.-H. Tsai, C.-C. Lai, L. Wan, T.-Y. Ho, C.-C. Hsieh, P.-D.L. Chao, Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds, *Antivir. Res.* 68 (2005) 36–42.
- [108] C.-Y. Wu, J.-T. Jan, S.-H. Ma, C.-J. Kuo, H.-F. Juan, Y.-S.E. Cheng, H.-H. Hsu, H.-C. Huang, D. Wu, A. Briki, Small molecules targeting severe acute respiratory syndrome human coronavirus, *Proc. Natl. Acad. Sci. Unit. States Am.* 101 (2004) 10012–10017.
- [109] E. Keyaerts, L. Vlijgen, C. Pannecouque, E. Van Damme, W. Peumans, H. Egberink, J. Balzarini, M. Van Ranst, Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle, *Antivir. Res.* 75 (2007) 179–187.
- [110] S. Schwarz, K. Wang, W. Yu, B. Sun, W. Schwarz, Emodin inhibits current through SARS-associated coronavirus 3a protein, *Antivir. Res.* 90 (2011) 64–69.
- [111] Y.A. Attia, M.M. Alagawany, M.R. Farag, F.M. Alkhathib, A.F. Khafaga, A.-M.E. Abdel-Moneim, K.A. Asiry, N.M. Mesalam, M.E. Shafi, M.A. Al-Harthi, Phylogenetic products and phytochemicals as a candidate strategy to improve tolerance to coronavirus, *Frontiers in Veterinary Science* 7 (2020) 1–18.
- [112] B.R. O'Keefe, B. Giomarelli, D.L. Barnard, S.R. Shenoy, P.K. Chan, J.B. McMahon, K.E. Palmer, B.W. Barnett, D.K. Meyerholz, C.L. Wohlford-Lenane, Broad-spectrum in vitro activity and in vivo efficacy of the antiviral protein griffithsin against emerging viruses of the family Coronaviridae, *J. Virol.* 84 (2010) 2511–2521.
- [113] P.W. Cheng, L.T. Ng, L.C. Chiang, C.C. Lin, Antiviral effects of saikogenapins on human coronavirus 229E in vitro, *Clin. Exp. Pathol.* 33 (2006) 612–616.
- [114] S. Wittemer, M. Ploch, T. Windeck, S. Müller, B. Drewelow, H. Derendorf, M. Veit, Bioavailability and pharmacokinetics of caffeoylquinic acids and flavonoids after oral administration of Artichoke leaf extracts in humans, *Phytomedicine* 12 (2005) 28–38.
- [115] R. Kaur, S.K. Manjal, R.K. Rawal, K. Kumar, Recent synthetic and medicinal perspectives of tryptanthrin, *Bioorg. Med. Chem.* 25 (2017) 4533–4552.
- [116] Y.-C. Tsai, C.-L. Lee, H.-R. Yen, Y.-S. Chang, Y.-P. Lin, S.-H. Huang, C.-W. Lin, Antiviral action of Tryptanthrin isolated from *Strobilanthes cusia* leaf against human coronavirus NL63, *Biomolecules* 10 (2020) 366.
- [117] C. Müller, W. Obermann, F.W. Schulte, K. Lange-Grünweller, L. Oestereich, F. Elgner, M. Glitscher, E. Hildt, K. Singh, H.-G. Wendel, Comparison of broad-spectrum antiviral activities of the synthetic roaglate CR-31-B (–) and the eIF4A-inhibitor Silvestrol, *Antivir. Res.* 175 (2020) 10470.

- [118] R. Yang, H. Liu, C. Bai, Y. Wang, X. Zhang, R. Guo, S. Wu, J. Wang, E. Leung, H. Chang, Chemical composition and pharmacological mechanism of qingfei paidu decoction and ma xing shi Gan decoction against coronavirus disease 2019 (COVID-19): in silico and experimental study, *Pharmacol. Res.* 157 (2020) 104820.
- [119] J.S. Mani, J.B. Johnson, J.C. Steel, D.A. Broszczak, P.M. Neilsen, K.B. Walsh, M. Naiker, Natural product-derived phytochemicals as potential agents against coronaviruses: a review, *Virus Res.* 284 (2020) 197989.
- [120] M. Russo, S. Moccia, C. Spagnuolo, I. Tedesco, G.L. Russo, Roles of flavonoids against coronavirus infection, *Chem. Biol. Interact.* 328 (2020) 109211.
- [121] M. Rehman, M.F. AlAjmi, A. Hussain, Natural Compounds as Inhibitors of SARS-CoV-2 Main Protease (3CLpro): A Molecular Docking and Simulation Approach to Combat COVID-19, *Current Pharmaceutical Design*, 2020.
- [122] Balachandar Vellingiri, Kaavya Jayaramayya, Mahalaxmi Iyer, Arul Narayanasamy, Vivekanandhan Govindasamy, Bupesh Giridharan, Singaravelu Ganesan, Anila Venugopal, Dhivya Venkatesan, Harsha Ganesan, Kamarajan Rajagopalan, Pattanathu K.S.M. Rahman, Ssang-Goo Cho, Nachimuthu Senthil Kumar, Mohana Devi Subramaniam, COVID-19: A promising cure for the global panic, *Sci. Total Environ.* 725 (138277) (2020) 138277, <https://doi.org/10.1016/j.scitotenv.2020.138277>.